- The pharmaceutical composition according to any one of claims 1-6, wherein the glucose-lowering agent and the lipid-improving agent are not mixed together but are administered independently to the mammal at the same time or at a different time within 48 hours.

C. **Claim Rejections - 35 USC § 102**

Claims 1-3, 7, 9-10 are rejected under 35 U.S.C 102(b) as being anticipated by Paterniti et al (WO9805331).

Applicant respectfully disagrees based on the following facts and requests re-consideration by the office

1. WO9805331 disclosed a pharmaceutical composition comprising two main components: (a) PPARγ (gamma) agonist and (b) PPARα (alpha) agonist including gemfibrozil or ciprofibrate.

   In an embodiment (page 13, line 19-29, as pointed out in the office's opinion), a long list of additional components was present in addition to the two main components (a) PPARγ (gamma) agonist and (b) PPARα (alpha) agonist. Metformin was among the long list.

   However, WO9805331 teaches that all pharmaceutical effects are resulted from the combination of (a) PPARγ (gamma) agonist and (b) PPARα (alpha) agonist. The combination of (a) PPARγ (gamma) agonist and (b) PPARα (alpha) agonist is seen as one entity and may be optionally combined with other components, including meformin. WO9805331 did not provide any teaching, suggestion, or anticipation that any one of the two main components, i.e., (a) PPARγ (gamma) agonist and (b) PPARα (alpha) agonist alone will exert any pharmaceutical effect when combined with metformin.

2. Present invention in 10/507,382 is related to a pharmaceutical composition contains only members of PPARα (alpha) agonist (gemfibrozil or ciprofibrate) and metformin. The present invention does not require PPARγ (gamma) agonist.

   Applicant of the present invention discovered that some of the PPARα (alpha) agonist such as gemfibrozil or ciprofibrate may be combined with meformin to exert unexpected pharmaceutical effect.

   It is therefore clear to a person skilled in the art that the two-component composition in the present invention, PPARα (alpha) agonist plus metformin, is completely different from the composition disclosed in WO98/05331, i.e., PPARγ (gamma) agonist and PPARα (alpha) agonist plus optional metformin.

   Applicant therefore believes that the present invention as presented in Claims 1-3, 7, 9-10 was not anticipated by Paterniti et al (WO9805331).

D. Claim Rejections - 35 USC § 103

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Paterniti et al (WO9805331).

Applicant respectfully disagrees based on the following facts and requests re-consideration by the office

1. WO9805331 disclosed a pharmaceutical composition comprising two main components: (a) PPARγ (gamma) agonist and (b) PPARα (alpha) agonist including gemfibrozil or ciprofibrate.

   In an embodiment (page 13, line 19-29, as pointed out in the office's opinion), a long list of additional components was present in addition to the two main components (a) PPARγ (gamma) agonist and (b) PPARα (alpha) agonist. Metformin was among the long list.

   However, WO9805331 teaches that all pharmaceutical effects are resulted from the combination of (a) PPARγ (gamma) agonist and (b) PPARα (alpha) agonist. The combination of (a) PPARγ (gamma) agonist and (b) PPARα (alpha) agonist is seen as one entity and may be optionally combined with other components, including meformin. WO9805331 did not provide any teaching, suggestion, or anticipation that any one of the two main components, i.e., (a) PPARγ (gamma) agonist and (b) PPARα (alpha) agonist alone will exert any pharmaceutical effect when combined with metformin. One skilled in the art would not be able to envisage the benefits of combining PPARα (alpha) agonist alone with metformin based on WO9805331.

2. Present invention in 10/507,382 is related to a pharmaceutical composition contains only members of PPARα (alpha) agonist (gemfibrozil or ciprofibrate) and metformin. The present invention does not require PPARγ (gamma) agonist.

   Applicant of the present invention discovered that some of the PPARα (alpha) agonist such as gemfibrozil or ciprofibrate may be combined with meformin to exert unexpected pharmaceutical effect.

   It is therefore clear to a person skilled in the art that the two-component composition in the present invention, PPARα (alpha) agonist plus metformin, is completely different from the composition disclosed in WO98/05331, i.e., PPARγ (gamma) agonist and PPARα (alpha) agonist plus optional metformin.

3. With the unexpected pharmaceutical effect of the present invention, the weight ratio of metformin and gemfibrozil becomes critical. As the office pointed out, Paterniti et al fails to disclose the weight ratio of the composition.

Applicant therefore believes that the present invention as presented in claim 4 can not be envisaged by Paterniti et al (WO9805331).

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Barelli et al (US 5922769) in view of Ko et al.

Applicant respectfully disagrees based on the following facts and requests re-consideration by the office.

1. As it was pointed out by Ko et al in the publication, "Dyslipidemia, one of the major risk factors for artherosclerosis, is common in diabetic patients. The most common lipid abnormalities among patients with non-insulin-dependent diabetes mellitus (NIDDM) are elevated levels of plasma triglyceride and reduced levels of high-density lipoprotein cholesterol (HDL-C)" and "Gemfibrozil is widely used to treat NIDDM patients with dyslipidemia, as it is one of the most effective agents in dealing with adverse triglycerides and HDL-C concentrations". It is very clear that gemfibrozil is used to treat dyslipidemia in patients with diabetes.

2. In Ko's publication, the efficacy of gemfibrozil in lowering triglyceride levels and raising HDL-C levels in patients with type 2 diabetes was confirmed and consistent with other studies, gemfibrozil failed to have any significant effect on plasma glucose levels.

3. As such, the use of a hypoglycemic agent and a lipid-improving agent together for treating diabetic patients with elevated triglyceride and elevated cholesterol has been in the context of using respective agents to correct respective abnormalities. One skilled in the art would not be able to envisage the present invention in 10/507,382 based on the teachings of Barelli et al and Ko et al, especially, the fact that gemfibrozil failed to have any significant effect on plasma glucose levels in patients with type 2 diabetes. In the present invention, combined administration of metformin and gemfibrozil produced an **unexpected synergistic reduction of plasma glucose concentrations**.

Applicant therefore believes that the present invention as presented in claim 8 can not be envisaged by combine the teachings of Barelli et al and Ko et al.

Applicant respectfully requests office to consider the above facts in the further examination.

Respectfully,

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